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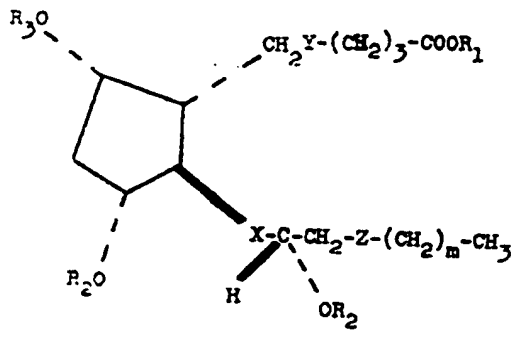
DERIVS

(54) IMPROVEMENTS IN OR RELATING TO DERIVS OF PROSTAGLANDINS AND THE PREPARATION THEREOF — FOR CONTROLLING OVULATION IN HUMANS AND ANIMALS

(71) We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel compounds and to compositions thereof which are useful for controlling the reproductive cycle in ovulating female mammals including humans and animals such as monkeys, rats, rabbits, dogs and cattle.

According to one feature of the invention there are provided novel compounds having the general formula:—



I

wherein R_1 is hydrogen, alkyl of 1 to 8 carbon atoms, inclusive, or a pharmacologically acceptable cation, R_2 and R_3 are hydrogen or alkanoyl of 1 to 8 carbon atoms, inclusive, with the proviso that when R_2 is alkanoyl, R_3 is also alkanoyl, m is zero or 2, and X, Y and Z are —CH_2CH_2—, or X is trans-CH=CH—, Y is cis-CH=CH—, and Z is —CH_2CH_2— or cis-CH=CH—.

In British Patent Specification No. 1,198,071 there are described and claimed optically active compounds extremely potent in causing various biological responses and having the general formula:—

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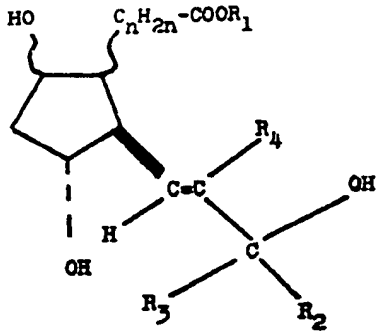
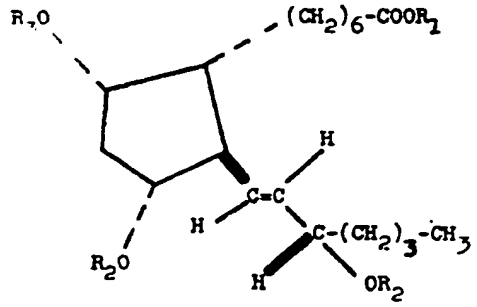


wherein ~ is a generic expression denoted an alpha or beta configuration for the attached moiety, R_1 is hydrogen, alkyl of 1 to 8 carbon atoms, inclusive, cycloalkyl of 3 to 10 carbon atoms, inclusive, aralkyl of 7 to 10 carbon atoms, inclusive, phenyl, or phenyl substituted by 1 to 3 chloro or alkyl of 1 to 4 carbon atoms, inclusive, R_2 is hydrogen or alkyl of 1 to 8 carbon atoms, inclusive, R_3 and R_4 are hydrogen or alkyl of 1 to 4 carbon atoms, inclusive, and C_nH_{2n} is alkylene of 1 to 8 carbon atoms, inclusive, and pharmacologically acceptable salts thereof when R_1 is hydrogen, excluding the compounds known as $PGF_{1\alpha}$ and $PGR_{1\beta}$ and their salts and esters.

Preferably in such compounds C_nH_{2n} is hexamethylene, R_4 is hydrogen, R_3 is hydrogen, R_1 is alkyl of 1 to 4 carbon atoms, inclusive, preferably methyl or R_1 is hydrogen, the $-C_nH_{2n}-COOR_1$ moiety is attached in alpha configuration and preferably also the —OH adjacent to $C_nH_{2n}-COOR_1$ is attached in alpha configuration.

It has now been found that the novel compounds of the general formula:—



II

wherein R_1, R_2 and R_3 are as defined above with the same proviso relating to R_3 and R_3 are useful also for controlling the reproductive cycle in ovulating female mammals thereby being useful in preventing pregnancy and in inducing labour in pregnant female mammals.

When R_2 and R_3 in a compound of formula I or formula II are both alkanoyl they can be the same or different.

These novel compounds of formulae I and II are some of the preferred compounds which are used in the methods of treatment described and claimed in our copending Application No. 39883/69 (Serial No. 1285371). These compounds are especially useful for the purposes described therein and are also useful for additional purposes as described further hereinafter.

Examples of alkyl of 1 to 8 carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and isomeric forms thereof.

Examples of alkanoyl of 1 to 8 carbon atoms, inclusive, are formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl, heptanoyl, octanoyl, and isomeric forms thereof.

Pharmacologically acceptable cations within the scope of R_1 in formulas I and II are quaternary ammonium ions or the cationic forms of a metal, ammonia, or an amine.

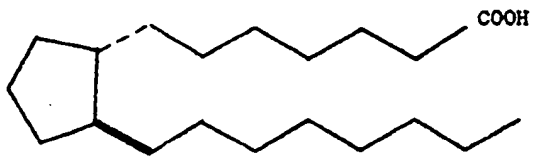
Especially preferred metal cations are those derived from the alkali metals, e.g.,

lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminium, zinc, and irons, are also within the scope R_1.

Pharmacologically acceptable amine cations also within the scope of R_1 in formulas I and II are those derived from primary, secondary, or tertiary amines. Examples of suitable amines are methylamine, dimethylamine, trimethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, and like aliphatic, cycloaliphatic, and araliphatic amines containing up to and including about 18 carbon atoms, as well as heterocyclic amines, e.g., piperidine, morpholine, pyrrolidine, piperazine, and lower-alkyl derivatives thereof, e.g., 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazine and 2-methylpiperidine, as well as amines containing water-solubilizing or hydrophilic groups, e.g., mono-, di-, and triethanolamine, ethyldiethanolamine, N-butylethanolamine, 2-amino-1-butanol, 2-amino-2-ethyl-1,3-propanediol, 2-amino-2-methyl-1-propanol, tris(hydroxymethyl)aminomethane, N-phenylethanolamine, N-(*p*-tert-amylphenyl)diethanolamine, galactamine, N-methylglucamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrine and procaine.

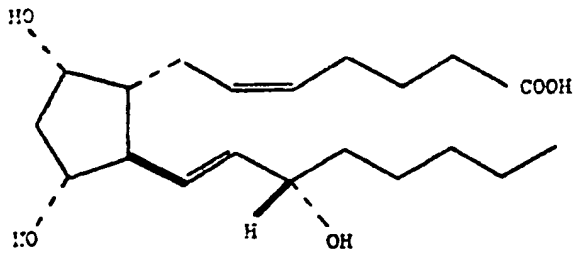
Examples of suitable pharmacologically acceptable quaternary ammonium cations within the scope of R_1 in formulas II and III are tetramethylammonium, tetraethylammonium, benzyltrimethylammonium and phenyltriethylammonium.

The compounds of formulas I and II are somewhat similar to certain of the natural prostaglandins. The latter are considered to be derivatives of prostanoic acid which has the following structure:



III

The naturally-occurring prostanoic acid derivative, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), has the following structure:



IV

The compound of formula I wherein R_1, R_2 and R_3 are hydrogen, and X is trans-CH=CH—, Y is cis-CH=CH—, and Z is —CH_2CH_2—, has the same structure as $PGF_{2\alpha}$ except that this novel formula I compound has one less carbon atom in the hydroxy-containing side chain (ω-nor) when m is zero, and one more carbon atom in the same chain (ω-homo) when m is 2. The other compounds encompassed by formula I are similarly related to the known prostanoic acid derivatives dihydro-$PGF_{1\alpha}$ and $PGF_{3\alpha}$. The compound of formula II wherein R_1, R_2 and R_3 are hydrogen has one less carbon (ω-nor) than the known $PGF_{1\alpha}$.

These ω-nor and ω-homo PGF_α compounds of formulas I and II are extremely potent in causing various biological responses of the general type caused by the corresponding natural PGF_α compounds. Regarding the biological responses caused by the natural PGF_α compounds, see, for example, Bergstrom et al., Pharmacol. Rev. 20, 1 (1968), and references cited therein.

Thus these formulas I and II compounds are useful for ensuring the regularity of menses and in place of oxytocin to induce labour in pregnant animals, including

man, cows, sheep, and pigs, at or near term, or in pregnant animals with intra-auterine death of the fetus from about 20 weeks to term. For this purpose, the compound is preferably infused intravenously at a dose 0.01 to 50 μg. per kg. of body weight per minute until or near the termination of the second stage of labour, i.e. expulsion of the fetus. These compounds are especially useful when the female is one or more weeks post-mature and natural labour has not started, or 12 to 60 hours after the membranes have ruptured and natural labour has not yet started.

The novel formula I and II compounds of this invention are useful in mammals, including man, as nasal decongestants. For this purpose, the compounds are used in a dose range of 10 μg to 10 mg. per ml. of a pharmacologically suitable liquid vehicle or as an aerosol spray, both for topical application.

The novel formula I and II compounds not only are potent in causing smooth muscle stimulation, but are also highly active in potentiating other known smooth muscle stimulators, for example, oxytocin, vasopressin, and the various ergot alkaloids including derivatives and analogs thereof. For these reasons, these novel compounds are useful in place of or in combustion with less than the usual amounts of these known smooth muscle stimulators, for example, to relieve the symptoms of paralytic ileus, to control or prevent atonic uterine bleeding after abortion or delivery, to aid in the expulsion of the placenta, and during the puerperium.

For these purposes, these novel formula I or II compounds are preferably first administered by intravenous infusion at a dose in the range 0.01 to 50 μg. per kg. of body weight per minute until the desired effect is obtained. Subsequent doses are given by intravenous, subcutaneous, or intra-muscular injection or infusion in the range 0.01 to 2 mg. per kg. of body weight per day, the exact dose depending on the age, weight, and condition of the patient or animal.

As described more fully below these novel formula I and II compounds are useful for controlling the reproductive cycle in ovulating female mammals, including humans and animals such as monkeys, rats, rabbits, dogs and cattle. For that purpose, the compounds are administered systemically at a dose level in the range 0.01 mg. to 20 mg. per kg. of body weight of the female mammal, advantageously during a span of time starting approximately at the time of ovulation and ending approximately at the time of menses or just prior to menses.

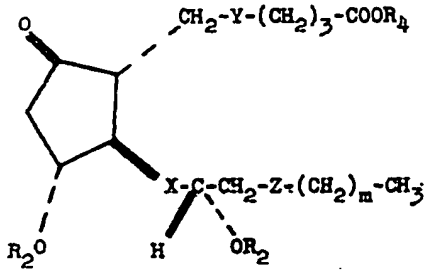
In spite of the apparent similarities of structure between the novel compounds of formulas I and II and the natural PGF_α compounds, i.e., dihydro-$PGF_{1\alpha}$, $PGF_{1\alpha}$, $PGF_{2\alpha}$, and $PGF_{3\alpha}$, the novel formula I and II compounds are surprisingly and quite unexpectedly more useful for one or more of the above illustrative purposes than the natural PGF_α compounds. The natural PGF_α compounds uniformly cause multiple responses even at low doses. For example, $PGF_{1\alpha}$ causes smooth muscle stimulation and a blood pressure rise at the same time that it acts to increase nasal patency. In striking contrast, the novel formula I and II compounds each are more specific in causing PGF_α-type biological responses. Each of these novel compounds is therefore surprisingly and unexpectedly more useful for the pharmacological purposes indicated above because each has a different and narrower spectrum of biological activity than the natural PGF_α compounds causing smaller and fewer undesired side effects than the natural compounds.

For the above purposes, the novel formula I and II compounds of this invention are administered in various ways. For example, as mentioned above, topical administration is the preferred route when the compound is used to promote nasal patency in cases of nasal congestion. Systemic administration, e.g., intravenous, subcutaneous, intramuscular, oral, rectal, vaginal, buccal, sublingual, and as sterile implants for prolonged action, are preferred for the other pharmacological purposes mentioned above.

For intravenous injection or infusion, sterile aqueous isotonic solutions are preferred. For that purpose, it is preferred because of increased water solubility that R_1 in the formula I or II compounds be hydrogen or a pharmacologically acceptable cation. For subcutaneous or intramuscular injection, sterile solutions or suspensions of the acid, salt, or ester form in aqueous or non-aqueous media are used. Tablets, capsules, and liquid preparations such as syrups, elixirs, and simple solutions, with the usual pharmaceutical carriers, are used for oral, buccal, or sublingual administration. For rectal or vaginal administration, suppositories or powders prepared as known in the art are used. For tissue implants, a sterile tablet or silicone rubber capsule containing the substance is used.

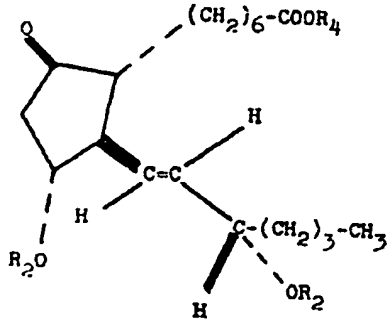
Accordingly the present invention also comprises a therapeutic composition comprising as the active ingredient a compound of the invention together with a pharmaceutically acceptable carrier.

The novel compounds of formula I are prepared by reducing the carbonyl group of the corresponding compounds of the formula:



V

Similarly, the novel compounds of formula II are prepared by reducing the carbonyl group of the corresponding compounds of the formula:



VI

In formulas V and VI, R_2, R_3, m, X, Y, and Z are as defined above, and R_4 is hydrogen or alkyl of one to 8 carbon atoms, inclusive.

These formula V and VI ketone intermediates are known in the art or are prepared by methods known in the art. See Beerthuis et al., Rec. Trav. Chim. 87, 461 (1968) for the compounds of formula V wherein R_2 and R_4 are hydrogen, m is zero or 2, and X is trans-CH=CH—, Y is cis-CH=CH—, and Z is —CH_2CH_2—, and for the compound of formula VI wherein R_2 and R_4 are hydrogen.

The formula V compounds wherein R_2 and R_4 are hydrogen, m is zero or 2, X is trans-CH=CH—, and Y and Z are cis-CH=CH—, are prepared from 5,8,11,14,17-nonadecapentaenoic acid (m=0) and 5,8,11,14,17-heneicosapentaenoic acid (m=2) as described by Struijk et al., Rec. Trav. Chim. 85, 1233 (1966), for the production of PGE_3 from 5,8,11,14,17-eicosapentaenoic acid. These C—19 and C—21 pentaenoic acids are prepared by saponification of the corresponding methyl esters which are prepared as described by the combination of Van der Steen et al., Rec. Trav. Chim. 82, 1015 (1963) and Pabon et al., Rec. Trav. Chim. 84, 1319 (1965), using in place of the initial reactant of Pabon et al., i.e., 1-bromo-2-pentyne, 1-bromo-2-butyne (C—199) and 1-bromo-2-hexyne (C—21). The latter two reactants are prepared from the corresponding known acetylenic alcohols by reaction with PBr_3.

The formula V compound wherein R_2 and R_4 are hydrogen, and X, Y, and Z are —CH_2CH_2— is prepared by reduction of the carbon-carbon double bonds of any of the formula V compounds wherein X is trans-CH=CH—, Y is cis-CH=CH—, and Z is —CH_2CH_2— or cis-CH=CH—. Alternatively, reduction of the carbon-carbon double bond of the formula VI compound wherein R_2 and R_4 are hydrogen leads to the corresponding formula V compound wherein X, Y, and Z are —CH_2CH_2— and m is zero. An alternative method for producing the formula V compound wherein X, Y, and Z are —CH_2CH_2— and m is 2 is reduction of ω-homo-PGE_1, a known compound. See Beerthuis et al., cited above.

The novel formula I and formula II compounds of this invention R_1 is alkyl are prepared by carbonyl reduction of the corresponding alkyl esters of the formula V or VI ketone intermediate. These alkyl esters are prepared by esterification of the corres-

ponding formula V or VI ketone intermediate wherein R_4 is hydrogen. Alternatively, the formula I or II alkyl esters are prepared by esterification of the corresponding formula I or II acids, i.e., wherein R_1 is hydrogen.

The novel formula I and formula II compounds of this invention wherein R_1 is a pharmacologically acceptable cation are preferably prepared by transformation of the corresponding formula I or II free acid (R_1=H) to the desired salt.

The novel formula I and formula II compounds of this invention wherein both R_2 are alkanoyl are prepared by carbonyl reduction of the corresponding alkanoyl derivatives of the formula V or VI ketone intermediates wherein both R_2 are alkanoyl. This produces a formula I or II dialkanoyl compound wherein R_3 is hydrogen. These dialkanoyl formula V and VI ketone intermediates are prepared by acylation of the corresponding formula V or VI ketone intermediate wherein both R_2 are hydrogen.

When it is desired that R_3 in the novel formula I or formula II compounds of this invention be alkanoyl, the formula I or II compound wherein R_3 is hydrogen is acylated. When both R_2 in the formula I or II compound are alkanoyl, the R_3 alkanoyl introduced can be the same or different as the R_2 alkanoyls. When both R_2 in the formula I or II compound are hydrogen, acylation changes all three hydroxy groups to the same alkanoyloxy group.

In a formula I or formula II compound, when R_1 is to be alkyl and R_3 and/or R_2 are to be alkanoyl, either or both the alkyl and the alkanoyls are added before or after the carbonyl reduction of the formula V or VI ketone intermediate.

An alternative method for producing formula I compounds wherein X, Y, and Z are $-CH_2CH_2-$ is reduction of the carbon-carbon double bonds of the formula I or II compound wherein at least one double bond is present, or by double bond reduction of the carbonyl reduction product ω-homo-PGE_1 or its alkyl and/or alkanoyl derivative.

Carbonyl reduction to produce the novel formula I and formula II compounds of this invention wherein R_3 is hydrogen is carried out by reacting the corresponding keto intermediates of formulas V and VI with any carbonyl reducing agent which does not react with the ester group or the carbon-carbon double bonds. Examples of such reducing agents are sodium or potassium borohydride and lithium aluminium (tri-tert-butoxy)-hydride.

These carbonyl reductions are carried out by methods known in the art for comparable reductions of prostanoic acid derivatives. See, for example, Bergstrom et al., Acta Chem. Scand. 16, 969 (1962) and Anggard et al., J. Biol. Chem. 239, 4101 (1964). Lower alkanols, e.g., methanol and ethanol, are preferred as reaction solvents, although other solvents, e.g., dioxane and diethylene glycol dimethyl ether are also used, especially in combination with the lower alkanol.

Although 0.25 molecular equivalent of the borohydride or lithium aluminium (tri-tert-butoxy)hydride reducing agent is sufficient to reduce one molecular equivalent of the formula V or formula VI ketone reactant, it is preferred to use an excess of the reducing agent, preferably 1 to 15 molecular equivalents of reducing agent per molecular equivalent of the ketone reactant. It is preferred to add a solution or suspension of the reducing agent to the ketone reactant, although the reverse order can also be used. A reaction temperature in the range 0° to 50°C. is usually satisfactory. At 25°C., the desired reaction is usually complete in 0.5 to 2 hours. The resulting complex compound is then transformed to the desired product in the usual manner by treatment with aqueous acid, advantageously dilute hydrochloric acid.

The desired formula I or formula II reduction product is isolated by conventional techniques, for example, evaporation of the reaction solvent and extraction of the residual aqueous mixture with a water-immiscible solvent, for example, diethyl ether. Evaporation of the latter solvent then gives the desired product.

These borohydride or lithium aluminium (tri-tert-butoxy)hydride reductions of the formula V and formula VI keto reactants each produce a mixture of an alpha-hydroxy compound and an isomeric (epimeric) beta-hydroxy compound. The alpha and beta components of these mixtures of isomeric hydroxy compounds are separated from each other by methods known in the art for the separation of analogous pairs of isomeric prostanoic acid derivatives. See, for example, Bergström et al., cited above, Granström et al., J. Biol. Chem. 240, 457 (1969), and Gréen et al., J. Lipid Research 5, 117 (1964). Especially preferred as separation methods are partition chromatographic procedures, both normal and reversed phase, thin layer chromatography, and countercurrent distribution procedures.

Catalytic hydrogenation or diimide are used to reduce carbon-carbon double bonds in the various unsaturated intermediates used to produce formula I compounds wherein X, Y, and Z are $-CH_2CH_2-$.

For catalytic hydrogenation, palladium catalysts, especially on a carbon carrier, are preferred. It is also preferred that the hydrogenation be carried out in the presence of an inert liquid diluent, for example, methanol, ethanol, dioxane and ethyl acetate. Hydrogenation pressures ranging from atmospheric to 50 p.s.i., and hydrogenation temperatures ranging from 10° to 100°C. are preferred. The reduced formula I acid or ester is isolated from the hydrogenation reaction mixture by conventional methods, for example, removal of the catalyst by filtration or centrifugation, followed by evaporation of the solvent. The desired hydrogenation product is purified by conventional techniques, advantageously by methods known to be useful for purification of the prostaglandins, especially thin layer chromatography. See, for example, Green et al., cited above.

For diimide reduction, the general procedure described by van Tamelen et al., J. Am. Chem. Soc., 83, 3726, (1961) is used. See also Fieser et al., "Topics in Organic Chemistry", Reinhold Publishing Corp., New York, pp. 432—434 (1963) and references cited therein for useful general procedures. The unsaturated acid or ester reactant is mixed with a salt of azodiformic acid, preferably an alkali metal salt such as the disodium or dipotassium salt, in the presence of an inert diluent, preferably a lower alkanol such as methanol or ethanol, and preferably in the absence of substantial amounts of water. At least one molecular equivalent of the azodiformic acid salt is used for each molecular equivalent of the reactant. The resulting suspension is then stirred, preferably with exclusion of oxygen, and the mixture is made acid, advantageously with a carboxylic acid such as acetic acid. When an acid reactant is used, that acid also serves to acidify an equivalent amount of the azodiformic acid salt. A reaction temperature in the range 10° to 40°C is usually suitable. Within that temperature range, the reaction is usually complete within less than 24 hours. The desired reduced product is then isolated by conventional methods, for example, evaporation of the diluent, followed by separation from inorganic materials by solvent extraction. The product is purified, if desired, as described above.

Esterification of the formula I or II acids or any of the other acid reactants is carried out by interaction of the acid with the appropriate diazohydrocarbon. For example, when diazomethane is used, the methyl esters are produced. Similar use of diazoethane, diazobutane, and 1-diazo-2-ethylhexane, for example, gives the ethyl, butyl, and 2-ethylhexyl esters, respectively.

Esterification with diazohydrocarbons is carried out by mixing a solution of the diazohydrocarbon in a suitable inert solvent, preferably diethyl ether, with the acid reactant, advantageously in the same or a different inert diluent. After the esterification reaction is complete, the solvent is removed by evaporation, and the ester purified if desired by conventional methods, preferably by chromatography. It is preferred that contact of the acid reactants with the diazohydrocarbon be no longer than necessary to effect the desired esterification, preferably one to ten minutes, to avoid undesired molecular changes. Diazohydrocarbons are known in the art or can be prepared by methods known in the art. See, for example, Organic Reactions, John Wiley & Sons Inc., New York, N.Y., Vol. 8, pp. 389—394 (1954).

An alternative method for esterification comprises transformation of the free acid to the corresponding silver salt, followed by interaction of that salt with an alkyl iodide. Examples of suitable iodides are methyl iodide, ethyl iodide, butyl iodide, isobutyl iodide and tert-butyl iodide. The silver salts are prepared by conventional methods, for example, by dissolving the acid in cold dilute aqueous ammonia, evaporating the excess ammonia at reduced pressure, and then adding the stoichiometric amount of silver nitrate.

Carboxyacylation of the hydroxy moieties in the keto reactants or in the formula I or II hydroxy compounds is accomplished by interaction of the hydroxy compound with a carboxyacylating agent, preferably the anhydride of an alkanoic acid of one to 8 carbon atoms, inclusive. For example, use of acetic anhydride gives the corresponding diacetate. Similar use of propionic anhydride, isobutyric anhydride, and hexanoic acid anhydride gives the corresponding carboxyacylates.

The carboxyacylation is advantageously carried out by mixing the hydroxy compound and the acid anhydride, preferably in the presence of a tertiary amine such as pyridine or triethylamine. A substantial excess of the anhydride should be used, preferably 10 to 10,000 moles of anhydride per mole of the hydroxy compound reactant. The excess anhydride serves as a reaction diluent and solvent. An inert organic diluent, for example, dioxane, can also be added. It is preferred to use enough of the tertiary amine to neutralize the carboxylic acid produced by the reaction, as well as any free carboxyl groups present in the hydroxy compound reactant.

The carboxyacylation reaction is preferably carried out in the range 0° to 100°C.

The necessary reaction time will depend on such factors as the reaction temperature, and the nature of the anhydride and tertiary amine reactants. With acetic anhydride, pyridine, and a 25°C reaction temperature, a 12 to 24-hour reaction time is used.

The carboxyacylated product is isolated from the reaction mixture by conventional methods. For example, the excess anhydride is decomposed with water, and the resulting mixture acidified and then extracted with a solvent such as diethyl ether. The desired carboxyacylate is recovered from the diethyl ether extract by evaporation. The carboxyacylate is then purified by conventional methods, advantageously by chromatography.

The formula I or II acids (R_1=hydrogen) are transformed to pharmacologically acceptable salts by neutralization with appropriate amounts of the corresponding inorganic or organic base, examples of which correspond to the cations and amines listed above. These transformations are carried out by a variety of procedures known in the art to be generally useful for the preparation of inorganic, i.e., metal or ammonium, salts, amine acid addition salts, and quaternary ammonium salts. The choice of procedure depends in part upon the solubility characteristics of the particular salt to be prepared. In the case of the inorganic salts, it is usually suitable to dissolve the formula I or II acid in water containing the stoichiometric amount of a hydroxide, carbonate, or bicarbonate corresponding to the inorganic salt desired. For example, such use of sodium hydroxide, sodium carbonate, or sodium bicarbonate gives a solution of the sodium salt of the prostanoic acid derivative. Evaporation of the water or addition of a water-miscible solvent of moderate polarity, for example, a lower alkanol or a lower alkanone, gives the solid inorganic salt if that form is desired.

To produce an amine salt, the formula I or II acid is dissolved in a suitable solvent of either moderate or low polarity. Examples of the former are ethanol, acetone, and ethyl acetate. Examples of the latter are diethyl ether and benzene. At least a stoichiometric amount of the amine corresponding to the desired cation is then added to that solution. If the resulting salt does not precipitate, it is usually obtained in solid form by addition of a miscible diluent of low polarity or by evaporation. If the amine is relatively volatile, any excess is easily removed by evaporation. It is preferred to use stoichiometric amounts of the less volatile amines.

Salts wherein the cation is quaternary ammonium are produced by mixing the formula I or II acid with the stoichiometric amount of the corresponding quaternary ammonium hydroxide in water solution, followed by evaporation of the water.

The invention is more fully understood by the following Examples.

EXAMPLE 1

ω-nor-$PGF_{2\alpha}$ (formula I: R_1, R_2 and R_3=H, m=0, X=trans-CH=CH—, Y=cis-CH=CH—, Z=—CH_2CH_2—).

A suspension of sodium borohydride (900 mg.) in 100 ml. of methanol at 5° to 10°C is added gradually with stirring during 2 minutes to a solution of ω-nor-PGE_2 (300 mg.) in 30 ml. of methanol at 0° to 5°C. Stirring is continued at 0° to 5°C for 20 minutes. The reaction mixture is then allowed to warm to 25°C., and is stirred at that temperature for one hour. The resulting mixture is then concentrated by evaporation to 2/3 of its original volume, mixed with 25 ml. of water, and evaporated further to remove the methanol. The aqueous solution which results is acidified with dilute hydrochloric acid and extracted three times with diethyl ether. The diethyl ether extracts are combined, washed with water, dried, and evaporated to give a mixture of the alpha and beta epimers of ω-nor-PGF_2.

The mixture of epimeric acids is subjected to reversed phase partition chromatography on silanized diatomaceous earth (Gas Chrom CLZ 100/120 mesh, a product of Applied Science Labs., State College, Pa.), using methanol-water (516 ml. —684 ml.) as the mobile phase and isooctanolchloroform (60 ml. —60ml.) as the stationary phase. The column support (500 g.) is mixed with 45 ml. of stationary phase, and is then packed into column form as a slurry with mobile phase. The mixture of epimeric ω-nor-PGF_2 acids is dissolved in 15 ml. of stationary phase and mixed with an additional 12 g. of the column support. The resulting slurry is poured onto the column. The column is then eluted with mobile phase, 50-ml. fractions of eluate being collected. The eluate fractions containing the alpha epimer, as shown by smooth muscle assays, are combined and evaporated to give ω-nor-$PGF_{2\alpha}$.

Following the procedure of Example 1, but using in place of the ω-nor-PGE_2, ω-nor-PGE_1, ω-nor-dihydro-PGE_1, ω-nor-PGE_3, ω-homo-PGE_2, ω-homo-dihydro-PGE_1, ω-homo-PGE_2, the methyl esters of each of those and also of ω-nor-PGE_2, the diacetates of each of those and also of ω-nor-PGE_2, and the methyl ester diacetates of each of those and also of ω-nor-PGE_2, there are obtained ω-nor-$PGF_{1\alpha}$, ω-nor-di-

hydro-$PGF_{1\alpha}$, ω-nor-$PGF_{3\alpha}$, ω-homo-$PGF_{3\alpha}$, ω-homo-dihydro-$PGF_{1\alpha}$ ω-homo-$PGF_{3\omega}$, the methyl esters of each of those PGF analogues and also of ω-nor-$PGF_{2\omega}$ the diacetates of each of those PGF analogues and also of ω-nor-$PGF_{2\alpha}$, and the methyl ester diacetates of each of those PGF analogues and also of ω-nor-$PGF_{2\alpha}$, respectively.

EXAMPLE 2

ω-nor-$PGF_{2\alpha}$ methyl ester (formula I: R_1=methyl, R_2 and R_3=H, m=O, X=trans-CH=CH—, Y=cis-CH=CH—, Z=—CH_2CH_2—).

ω-nor-$PGF_{2\alpha}$ (10 mg.) is dissolved in a mixture of methanol and diethyl ether (1:1). A diethyl ether solution of diazomethane (1 g.) is added, and the mixture is allowed to stand at about 25° for 5 minutes. The reaction mixture is then evaporated to dryness to give the methyl ester of ω-nor-$PGF_{2\alpha}$.

Following the procedure of Example 2 but using in place of diazomethane, diazoethane, diazobutane, and 1-diazo-2-ethylhexane, there are obtained the ethyl, butyl, and 2-ethylhexyl esters, respectively.

Also following the procedure of Example 2, ω-nor-$PGF_{1\alpha}$, ω-nor-dihydro-$PGF_{3\alpha}$, ω-nor-$PGF_{3\alpha}$, ω-homo-$PGF_{3\alpha}$, ω-homo-dihydro-$PGF_{1\alpha}$, ω-homo-$PGF_{3\alpha}$, the diacetates and triacetates of each of those and also of ω-nor-$PGF_{2\alpha}$ are each transformed to the corresponding methyl, ethyl, butyl, and 2-ethylhexyl esters.

EXAMPLE 3

ω-nor-$PGF_{2\alpha}$ triacetate (formula I: R_1=H, R_2 and R_3=acetyl, m=O, X=trans-—CH=CH—, Y=cis-CH=CH—, Z=—CH_2CH_2—).

ω-nor-$PGF_{2\alpha}$ (10 mg.) is mixed with acetic anhydride (3 ml.) pyridine (3 ml.), and the mixture is allowed to stand at 25°C for 18 hours. The reaction mixture is then cooled with ice, diluted with water, and acidified with dilute hydrochloric acid to pH 1. That mixture is then extracted three times with diethyl ether. The diethyl ether extracts are combined, and washed successively with dilute hydrochloric acid, dilute aqueous sodium bicarbonate solution, and water. The diethyl ether is then evaporated to give ω-nor-$PGF_{2\alpha}$ triacetate.

Following the procedure of Example 3, but replacing the acetic anhydride with propionic anhydride, isobutyric anhydride, and hexanoic acid anhydride, the corresponding tricarboxyacyl derivatives of ω-nor-$PGF_{1\alpha}$ were obtained.

Also following the procedure of Example 3, ω-nor-$PGF_{1\alpha}$, ω-nor-dihydro-$PGF_{1\alpha}$, ω-nor-$PGF_{3\alpha}$, ω-homo-$PGF_{3\alpha}$, ω-homo-dihydro-$PGF_{1\alpha}$, ω-homo-$PGF_{3\alpha}$, and the methyl esters of each of those and also of ω-nor-$PGF_{2\alpha}$ are each transformed to the corresponding triacetates, tripropionates, triisobutyrates, and trihexanoates.

Also following the procedure of Example 3, the diacetates of ω-nor-$PGF_{1\alpha}$, ω-nor-dihydro-$PGF_{1\alpha}$, ω-nor-$PGF_{3\alpha}$, ω-nor-$PGF_{2\alpha}$, ω-homo-dihydro-$PGF_{1\alpha}$, ω-homo-$PGF_{2\alpha}$, and ω-homo-$PGF_{3\alpha}$ are each transformed to the corresponding triacetates, propionate-diacetates, butyrate-diacetates, and hexanoate-diacetates.

EXAMPLE 4

ω-nor-$PGF_{2\alpha}$ sodium salt (Formula I: R_1=Na^+, R_2 and R_3=H, m=O, X=trans-CH=CH—, Y=cis-CH=CH—, Z=—CH_2CH_2—).

ω-nor-$PGF_{2\alpha}$ (10 mg.) is dissolved in 10 ml. of water-ethanol (1:1). The solution is cooled to about 10°C and is neutralized with an equivalent amount of 0.1 N aqueous sodium hydroxide solution. Evaporation to dryness gives ω-nor-$PGF_{2\alpha}$ sodium salt.

Following the procedure of Example 4 but using potassium hydroxide, calcium, hydroxide, tetramethylammonium hydroxide, and benzyltrimethylammonium hydroxide, in place of sodium hydroxide there are obtained the corresponding salts of ω-nor-$PGF_{2\alpha}$.

Also following the procedure of Example 4, each of the other PGF analogues and the diacyl and triacyl PGF analogues mentioned above are transformed to the corresponding sodium, potassium, calcium, tetramethylammonium, and benzyltrimethylammonium salts.

EXAMPLE 5

ω-nor-dihydro-$PGF_{1\alpha}$ (Formula I: R_1, R_2, and R_3=H, m=O, X, Y, and Z=—CH_2CH_2—).

A solution of ω-nor-$PGF_{1\alpha}$ (100 mg.) in 8 ml. of ethyl acetate is shaken with hydrogen at about one atmosphere pressure and 25°C in the presence of 5% palladium on charcoal (15 mg.). One equivalent of hydrogen is adsorbed in about 100 minutes. The hydrogenation is stopped, and the catalyst is removed by filtration. Evaporation

of the filtrate gives a gummy residue which is chromatographed on silica gel with ethyl acetate and hexane (3.1) to give ω-nor-dihydro-$PGF_{1\alpha}$.

Following the procedure of Example 5, ω-nor-$PGF_{2\alpha}$ and ω-nor-$PGF_{3\alpha}$ are each transformed to ω-nor-dihydro-$PGF_{1\alpha}$ using 2 and 3 equivalents of hydrogen, respectively.

Also following the procedure of Example 5, ω-homo-$PGF_{2\alpha}$ and ω-homo-$PGF_{3\alpha}$ are each transformed to ω-homo-dihydro-$PGF_{1\alpha}$ using 2, and 3 equivalents of hydrogen respectively.

Also following the procedure of Example 5 and using the appropriate amount of hydrogen, each of the unsaturated alkyl esters and di- and trialkanoates mentioned above is transformed to the corresponding dihydro-PGE_1 analogue and dihydro-$PGF_{1\alpha}$ analogue.

EXAMPLE 6

ω-nor-dihydro-$PGF_{1\alpha}$ (Formula I: R_1, R_2, and R_3=H, m=0, X, Y, and Z=—CH_2CH_2—).

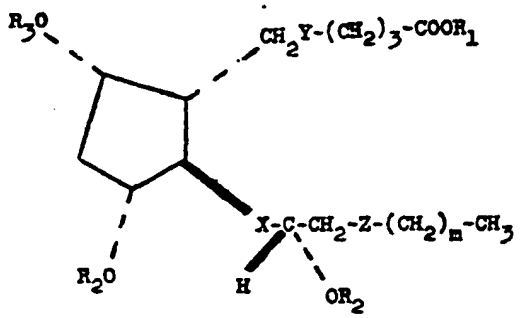
ω-nor-$PGF_{1\alpha}$ (50 mg.) is dissolved in 10 ml. of absolute ethanol. Air is flushed from the reaction vessel with a stream of dry nitrogen gas, and is excluded thereafter by maintaining a slight positive pressure of nitrogen in the reaction vessel. A suspension of 50 mg. if disodium azodiformate in 5 ml. of absolute ethanol is added, and the resulting mixture is stirred at about 25°C and made acid with a few drop of glacial acetic acid. Stirring at 25°C is continued for 8 hours. The reaction mixture is then evaporated to dryness. The resulting residue is dissolved in a mixture of diethyl ether and water. The diethyl ether layer is separated, dried with anhydrous sodium sulphate, and evaporated at reduced pressure to give ω-nor-dihydro-$PGF_{1\alpha}$ with substantially the same properties as the material prepared according to Example 5.

Following the procedure of Example 6, each of the unsaturated PGF analogues reduced according to the procedure of Example 5 is also reduced according to the procedure of Example 6 to give the corresponding dihydro-$PGF_{1\alpha}$ analogue with substantially the same properties as the materials prepared according to Example 5. In those reductions, amounts of disodium azodiformate appropriate to the number of carbon-carbon double bonds are used.

Compounds of the general formulae I and II and the specific compounds prepared in Examples 1 to 6 when administered therapeutically can also be formulated in compositions such as those described in our copending Application No. 39883/69 (Serial No. 1285371).

WHAT WE CLAIM IS:—

1. A compound of the formula:



wherein R_1 is hydrogen, alkyl of one to 8 carbon atoms, inclusive, or a pharmacologically acceptable cation, R_2 and R_3 are hydrogen or alkanoyl of one to 8 carbon atoms, inclusive, with the proviso that when R_3 is alkanoyl, R_2 is also alkanoyl, m is zero or 2, and X, Y, and Z are —CH_2CH_2—, or X is trans-CH=CH—, Y is cis-CH=CH— and Z is —CH_2CH_2— or cis-CH=CH—.

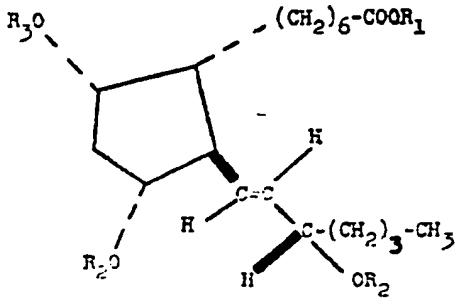
2. A compound according to claim 1, wherein R_1, R_2, and R_3 are hydrogen.

3. A compound according to claim 2, wherein X, Y, and Z are —CH_2CH_2—.

4. A compound according to claim 2, wherein X is trans-CH=CH—, Y is cis-CH=CH—, and Z is —CH_2CH_2—.

5. A compound according to claim 2, wherein X is trans-CH=CH—, and Y and Z are cis-CH=CH—.

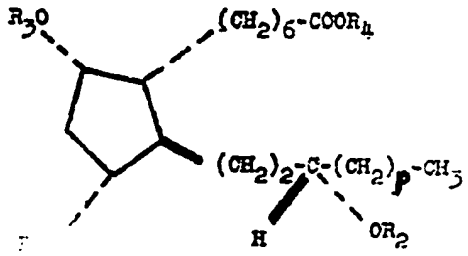
6. A compound of the formula:



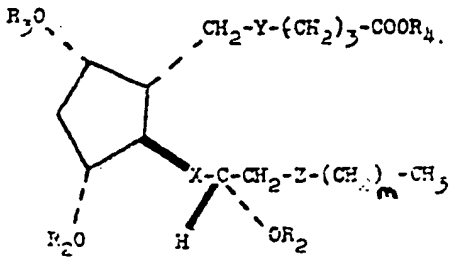
wherein R_1 is hydrogen, alkyl of one to 8 carbon atoms, inclusive, or a pharmacologically acceptable cation, and R_2 and R_3 are hydrogen or alkanoyl of one to 8 carbon atoms, inclusive, with the proviso that when R_3 is alkanoyl, R_2 is also alkanoyl.

7. A compound according to claim 6, wherein R_1, R_2, and R_3 are hydrogen.

8. A process for producing a compound of the formula:

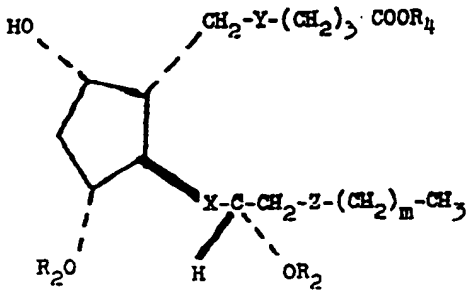


wherein R_2 and R_3 are hydrogen or alkanoyl of one to 8 carbon atoms, inclusive, with the proviso that when R_3 is alkanoyl, R_2 is also alkanoyl, R_4 is hydrogen or alkyl of one to 8 carbon atoms, inclusive, and p is 3 or 5, which comprises reducing the carbon-carbon double bonds of a compound of the formula:

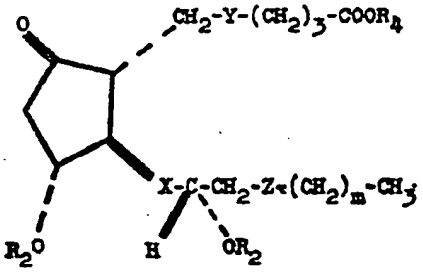


wherein R_2, R_3, and R_4 are as defined above, m is zero or 2, and X is trans-CH=CH— and Y and Z are —CH_2CH_2—, or X is trans-CH=CH—, Y is cis-CH=CH—, and Z is —CH_2CH_2— or cis-CH=CH—.

9. A process for producing a compound of the formula:

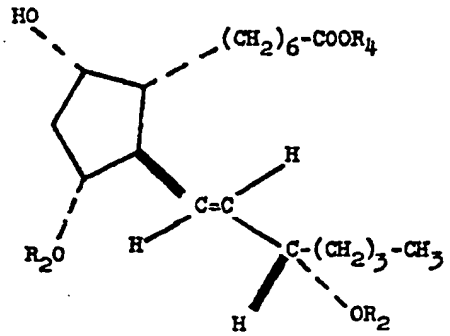


wherein R_2 is hydrogen or alkanoyl of one to 8 carbon atoms, inclusive, R_4 is hydrogen or alkyl of one to 8 carbon atoms, inclusive, m is zero or 2, and X, Y and Z are $-CH_2CH_2-$, or X is trans-CH=CH—, Y is cis-CH=CH—, and Z is $-CH_2CH_2-$ or cis-CH=CH—, which comprises reducing the carbonyl group of a compound of the formula:

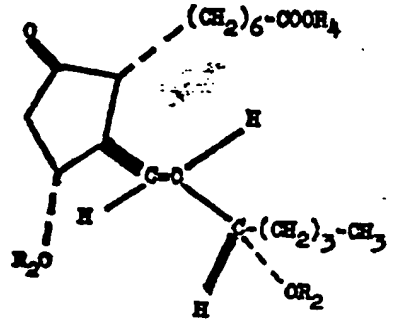


wherein R_2, R_4, m, X, Y and Z are as defined above.

10. A process for producing a compound of the formula:



wherein R_2 is hydrogen or alkanoyl of one to 8 carbon atoms, inclusive, and R_4 is hydrogen or alkyl of one to 8 carbon atoms, inclusive, which comprises reducing the carbonyl group of a compound of the formula:



wherein R_2 and R_4 are as defined above.

11. A process for the preparation of a compound as claimed in any of claims 1 to 7 substantially as herein described with reference to Examples 1 to 6.

12. A compound as claimed in any of claims 1 to 7 when prepared by a process as claimed in claims 8 to 11.

13. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1 to 7 or 12 together with a pharmaceutically acceptable carrier.

14. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1 to 7 or 12 substantially as herein described.

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